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Series editor: James T. Li, MD, PhD

Cutaneous drug reactions

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Activity Objectives

1. To be able to recognize the most common cutaneous drug reaction.
2. To be able to identify the clinical characteristics of acute generalized exanthematous pustulosis (AGEP).
3. To be able to list drugs commonly associated with Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

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CLINICAL VIGNETTE

A 49-year-old woman with diabetes underwent a midline inguinal hernia repair. She was later admitted for a wound infection with sinus tract drainage into her peritoneum requiring another abdominal surgery. She received a dose of cefazolin intraoperatively followed by ticarcillin/clavulanate and vancomycin. In addition, she was started on fluoxetine for depression and hydrocodone as needed for pain. Three days later, cultures obtained at the time of surgery revealed methicillin-resistant *Staphylococcus aureus*; the ticarcillin/clavulanate was discontinued, and she remained on vancomycin. On postoperative day 9, she received a dose of fluconazole for oral thrush, and 30 minutes later, she noted diffuse itching. Within hours, she experienced a diffuse and painful vesicular eruption. The allergy and immunology service was consulted for evaluation of fluconazole allergy. Physical examination was notable for scattered erythematous papules, a few targetoid lesions (see Fig E1 in this article's Online Repository at www.jacionline.org), and tense blisters (see Fig E2 in this article's Online Repository at www.jacionline.org) involving the arms, legs, palms, labia, and tongue with a few erosions on the gingiva.

The full version of this article, including a review of relevant issues to be considered, can be found online at www.jacionlineorg. If you wish to receive CME or MOC credit for the article, please see the instructions above.

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REVIEW

Adverse drug reactions are defined by the World Health Organization as any noxious, unintended, and undesired effect of a drug that occurs at doses used for prevention, diagnosis, or treatment. Drug-induced allergic reactions (immunologically mediated adverse drug reactions) typically account for a minority of all adverse drug reactions. However, most cutaneous reactions to drugs are indeed drug-induced allergic reactions. Drug-induced allergic reactions can present with a myriad of cutaneous manifestations (Table E1). Recognition of the various cutaneous patterns can aid in both diagnosis and management of drug-induced allergic reactions. Some cutaneous reactions can have mixed immunopathogenesis (eg, urticaria), adding confusion to the clinical picture. Although a discussion of all of the various cutaneous drug reactions is beyond the scope of this review, this topic has been extensively reviewed elsewhere.[E1-E3] Several of the more common, as well as serious, cutaneous drug reactions will be reviewed here.

Exanthems

The most common cutaneous manifestation of drug-induced allergic reactions is a generalized exanthem (also known as maculopapular eruption), which can be caused by hundreds of medications, with some of the more common culprits being aminopenicillins, cephalosporins, sulfonamide antibiotics, antiepileptics, and allopurinol. The immunopathology of many exanthems is consistent with delayed-type hypersensitivity reactions. Maculopapular exanthems have a mononuclear cell infiltrate with a predominance of $CD4^+$ or $CD8^+$ T cells. These lesions are pruritic, often beginning as macules that can evolve into papules and eventually can coalesce into plaques. Some exanthems can present as erythroderma. Drug-induced exanthems are nearly always pruritic and typically start on the trunk and spread outward to the extremities in a bilateral symmetric pattern. Many drug-induced exanthems are considered delayed-type hypersensitivity reactions and typically evolve after several days of taking the offending drug. A key clinical point regarding drug-induced exanthems is that they do not evolve into anaphylactic reactions because they are not IgE-mediated reactions. Another key point is that with resolution of an exanthem, scaling can occur, which is a benign feature. This should be distinguished from the type of epidermal detachment seen in severe cutaneous reactions that occurs early in the reaction.

Urticaria and angioedema

Urticaria and angioedema are the most common manifestations of IgE-mediated drug allergy; can be caused by hundreds of medications, most commonly β-lactam antibiotics; and are easily recognized by allergists. However, a key point to recognize is that non–IgE-mediated drug-induced allergic reactions can also manifest with urticaria and angioedema. Urticaria is the most common cutaneous manifestation of serum sickness; however, the presence of maculopapular lesions on the sides of the fingers and toes or a serpiginous distribution of such lesions along the lateral aspects of both soles might be more specific for serum sickness. Urticaria and angioedema can result from complement activation or be bradykinin mediated (eg, angiotensin converting enzyme [ACE] inhibitor–induced angioedema). IgE-mediated drug reactions typically occur within minutes of exposure to the drug in a previously sensitized patient. The delay in onset from drug exposure for non–IgE-mediated urticaria and angioedema is longer, days to even years, as in the case of ACE inhibitor–induced angioedema.

Fixed drug eruptions

Fixed drug eruptions are a relatively common cutaneous drug reaction that can often go unrecognized by patients and physicians. The immunopathology of fixed drug eruptions is most consistent with a delayed hypersensitivity reaction involving intraepidermal $CD8^+$ T cells. The lesions rapidly recur (within a few hours) at the same skin or mucosal site on reintroduction of the causative drug.[E4] Fixed drug eruptions are pleomorphic and can present as eczematous lesions, papules, vesicles, or urticaria and occasionally involve the oral mucosa. Lesions are often round or oval, sharply demarcated, red to livid, slightly elevated plaques ranging from a few millimeters to several centimeters in diameter. The timing for fixed drug eruptions is typically within 1 to 2 weeks of drug exposure but might recur more rapidly with subsequent re-exposure. Common anatomic locations for fixed drug eruptions include the lips, hands, and genitalia (especially in men). Fixed drug eruptions can occur with a number of medications, including tetracycline, nonsteroidal anti-inflammatory drugs (NSAIDs), and carbamazepine.

Pustular drug eruptions

Pustules can be another manifestation of drug-induced allergic reactions. The most common pustular drug reaction encountered by allergists is glucocorticoid-induced acne (steroid acne), an adverse drug reaction. Small pustules on the trunk, shoulders, and upper arms sparing the face characterize steroid acne. Acne lesions typically occur within a few weeks of therapy. Androgens (used for hereditary angioedema) can be another cause of drug-induced acne in the allergy clinic; however, several other agents can cause acne, including lithium, phenytoin, isoniazid, and sirolimus, which has a high rate of causing acne. Acute generalized exanthematous pustulosis (AGEP) is a rare type of drug eruption that begins with erythema or edema in the intertriginous areas or face. Afterward, fine nonfollicular sterile pustules develop. Fever, neutrophilia, and eosinophilia can also be present. Atypical target lesions, blisters, and mucosal involvement (mostly oral and mild) are uncommon but can be confused with Stevens-Johnson syndrome (SJS).[E5] AGEP should be distinguished from other causes of infectious pustules, such as candidiasis, gonococcemia, impetigo, and bacterial folliculitis. The immunopathology of AGEP is consistent with a delayed-type hypersensitivity related to $CD4^+$ T cells that produce high levels of IL-8. AGEP can develop within days for some drugs (eg, antibiotics) or over weeks with other medications (eg, calcium-channel blockers).

Vesicular/bullous drug eruptions

Drug-induced allergic reactions can also present with vesicles or bullae. Some of these reactions are relatively benign and self-limited, whereas others are classified as severe cutaneous adverse reactions (SCARs). Flaccid blisters can occur with drug-induced pemphigus and are often caused by drugs containing a thiol group (eg, captopril and penicillamine). The mechanism of drug-induced pemphigus is not clear but might be related to pharmacologic effects on enzymes or cytokine activation leading to acantholysis. Tense blisters can be due to drug-induced bullous

pemphigoid and can be caused by several drugs, including ACE inhibitors, furosemide, penicillin, and sulfasalazine. Drug-induced bullous pemphigoid might be due to multiple mechanisms, including autoantibodies to basement membrane zone antigens, such as BP180, a common bullous pemphigoid antigen. Linear IgA bullous disease causes a clinically similar eruption, and vancomycin is the most commonly incriminated drug. Linear IgA bullous disease is an autoimmune disorder with linear IgA deposition typically localized to the basement membrane zone against antigenic targets, including BP180.

Patients with erythema multiforme major (EMM) have target lesions with or without blisters. Clinically, EMM is similar to SJS, but there are important differences.[E6] EMM causes symmetric, mainly acral lesions, and mucosal involvement is less severe and less frequently involves 2 or more mucosal lesions. EMM occurs mainly after herpes simplex infection and less frequently is drug induced, and the prognosis is usually benign. In addition to SJS, other drug reactions considered SCARs, such as toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS), can also present with vesicular or bullous lesions.

SCARs

SCARs are composed of 3 distinct types of cutaneous reactions with systemic manifestations and include the previously mentioned AGEP, SJS/TEN, and DRESS. Recently, pharmacogenomic studies have identified several specific HLA alleles that have been associated with specific drugs and SCARs. Carbamazepine-induced SCARs have been associated with HLA-A*3101 in European subjects and HLA-B*1502 in Asian subjects of Han Chinese descent. Allopurinol-induced SCARs have been associated with HLA-B*5801 in patients of Asian and European descent. Abacavir hypersensitivity syndrome has been associated with HLA-B*5701 in patients with multiple ethnicities.

SJS/TEN

SJS and TEN are now considered part of a single disease spectrum. The primary epidermal pathology in patients with TEN is large-scale epidermal death, the result of apoptosis. The exact mechanism of apoptosis in patients with TEN is unknown but might involve granzymes, granulysin, TNF, and Fas ligand as effectors of apoptosis. SJS is usually classified as having less than 10% total body surface area involvement, whereas involvement of greater than 30% is classified as TEN. The majority of cases of SJS are drug induced, and TEN is almost always drug induced. Key clinical features of SJS/TEN include a triad of mucous membrane erosions, target lesions, and epidermal necrosis with detachment.[E7] A prodromal phase of fever, cough, and malaise can precede cutaneous findings by a few weeks. Target lesions can begin as 3-ringed iris lesions and evolve to purpuric 2-ringed lesions. Blisters can occur in patients with SJS/TEN and are typically flaccid. SJS/TEN lesions often first appear on the trunk and then rapidly spread to the face, neck, and extremities, usually peaking in 4 days. Painful mucosal lesions can involve the lip, oral cavity, conjunctiva, nasal cavity, urethra, and vagina. Corneal involvement, when present, might result in ulceration, perforation, and sclerotic corneal changes and requires monitoring by an ophthalmologist. Gastrointestinal, hepatic, pulmonary, and renal involvement can also occur with SJS/TEN. Although numerous drugs have been implicated as causes of SJS/TEN, high-risk drugs include sulfonamide antibiotics, cephalosporins, carbamazepine, phenytoin, oxicam NSAIDs, nevirapine, lamotrigine, sertraline, pantoprazole, and tramadol.[E8]

DRESS

DRESS syndrome is a drug-induced, multiorgan inflammatory response that can be life-threatening. Although the terminology used for DRESS has changed over the years, these syndromes are characterized by multiorgan involvement, including varying cutaneous eruptions (eg, exanthems, vesicles, and target lesions), fever, eosinophilia (most but not all cases), hepatic dysfunction, renal dysfunction, and lymphadenopathy.[E9] A key point in some cases of DRESS is that patients can have a fairly diffuse facial edema that can be mistaken for angioedema. Additional features of DRESS can include multiorgan involvement, including the lungs, heart, joints, and brain, and in some cases hypogammaglobulinemia. The immunopathogenesis of DRESS is not well understood. Failure of drug detoxification pathways leading to an accumulation of harmful metabolites has been hypothesized to explain DRESS from anticonvulsants. Drug-specific T cells and reactivation of human herpesvirus 6 can also be involved with the pathogenesis of DRESS. A scoring system for classifying DRESS as definite, probable, possible, or "no case" has been developed based on several clinical features, including fever of greater than 38°C, enlarged lymph nodes, eosinophilia, atypical lymphocytes, skin involvement, organ involvement, resolution in 15 days or longer, and evaluation for other potential causes.[E10] Numerous medications have been implicated in DRESS, including anticonvulsants, sulfonamides, allopurinol, minocycline, dapsone, abacavir, nevirapine, vancomycin, and NSAIDs. Key distinguishing features of DRESS compared with other drug-induced allergic reactions are that DRESS develops usually 2 to 8 weeks after the drug is started and symptoms can worsen or persist for weeks or even months after the drug has been discontinued.

Role of skin biopsy

For many cutaneous drug reactions, history and physical examination are sufficient to make the diagnosis and identify the culprit drug. However, in cases in which the diagnosis is less clear, skin biopsies can be helpful in identifying the type of drug reaction, as well as excluding other cutaneous diseases. Skin biopsies can aid in differentiating vasculitis, bullous diseases, and contact dermatitis. The best lesions to biopsy are evolving or recent skin lesions, and the biopsy should be performed at the edge of the lesion. Immunofluorescence stains are important, particularly in the evaluation of bullous lesions. A key point is that there are no absolute histologic criteria for the diagnosis of drug-induced eruptions, and therefore a skin biopsy might not definitively exclude alternative causes. Also, the histopathologic features of interface dermatitis, spongiosis, and tissue eosinophilia are not specific and can be seen with other cutaneous diseases.

Diagnostic testing

Diagnostic testing for cutaneous drug reactions is relatively limited because of the lack of tests with sufficient negative (or positive) predictive values. Immediate skin testing with nonirritating concentrations can be helpful in cases of suspected

IgE-mediated urticaria/angioedema to agents such as antibiotics, with penicillin being the only drug with well-defined negative predictive values. Delayed intradermal tests might be helpful in maculopapular exanthems, and results are often positive to antibiotics, heparin, or radiocontrast media. Patch testing has been found to be most useful in patients with fixed drug eruptions (when tested at the residual site), as well as in some patients with AGEP. Patch testing in patients with SCARs is controversial. A number of *in vitro* tests, including specific IgE tests, lymphocyte transformation, and basophil activation tests, have been studied in drug allergy centers, with varying results in terms of specificity and sensitivity. The use of commercially available *in vitro* tests deserves further study before they can be accepted as diagnostic tools. Finally, drug challenges (immediate and delayed) are useful tools for patients with histories suggesting a low pretest probability of reacting but are usually contraindicated in patients with SCARs.

THE CASE REVISITED

The appearance of a pruritic rash with vesicular and targetoid eruptions was concerning for a drug reaction. The onset of pruritus within 30 minutes of fluconazole might have been due to an IgE-mediated reaction; however, the appearance of vesicular reactions within hours would make it highly unlikely that the fluconazole was the culprit drug. The β-lactams were considered unlikely culprits because of their discontinuation 6 to 9 days before the eruption. Hydrocodone is a common cause of pruritus from pseudoallergic reactions, but vesicular eruptions would be rare. Fluoxetine is also rarely the cause of vesicular drug eruptions. Vancomycin is the most common cause of linear IgA bullous disease, which might also affect mucosal surfaces and could also cause DRESS.[E11] SJS was also a consideration because of the targetoid lesions and involvement of 2 mucosal sites. We recommended discontinuation of vancomycin. Results of a complete blood count with differential and comprehensive metabolic panel were normal. A skin biopsy was performed with immunofluorescence, and results were consistent with a diagnosis of linear IgA bullous dermatitis. She was started on systemic steroids because of worsening of the eruptions and painful lesions and had rapid improvement and eventual resolution of her symptoms.

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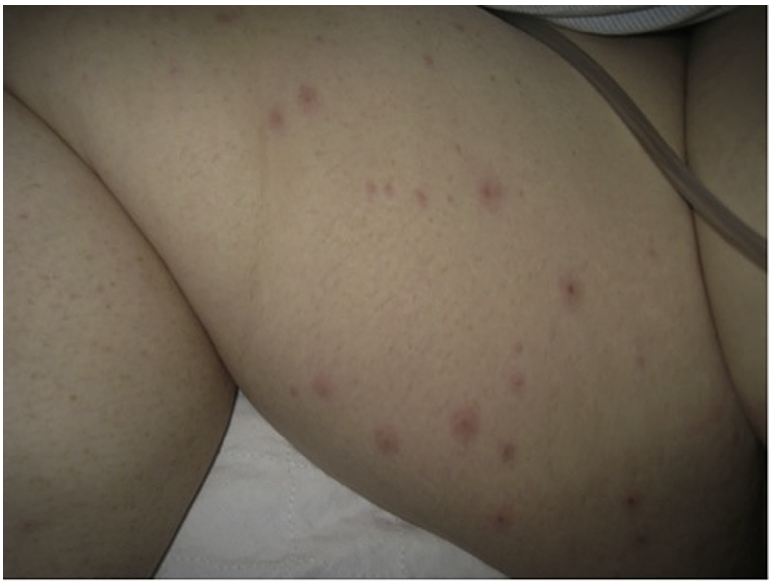

FIG E1. Papular and targetoid lesions on the thigh (photo courtesy of Gabriela Blanco, MD).

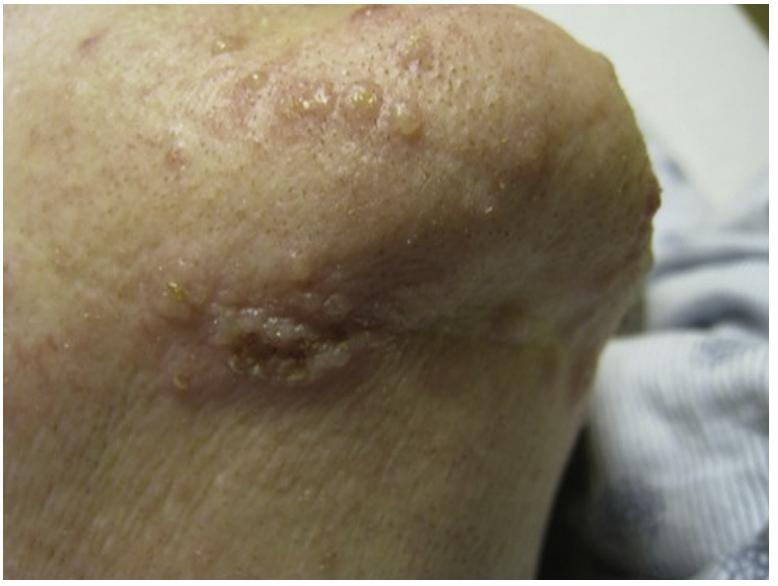

FIG E2. Tense vesicular lesions (photo courtesy of Gabriela Blanco, MD).

TABLE E1. Spectrum of cutaneous drug reactions

Common cutaneous drug reactions
Exanthems
Urticaria
Angioedema
Fixed drug eruption
Pruritus
Acneform
SCARs
DRESS
SJS/TEN
AGEP
Less common cutaneous drug reactions
Acanthosis nigricans
Alopecia
Aphthous stomatitis
Black hairy tongue
Bullous eruptions
Erythema nodosum
Exfoliative dermatitis
Gingival hyperplasia
Lichenoid eruptions
Lupus erythematosus
Phototoxic/photoallergic
Pigmentation
Pityriasis rosea–like eruptions
Psoriasis
Purpura
Vasculitis